Navigating non-randomized comparisons: from pitfalls to practice

Workshop on the use of external data; EMA
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EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
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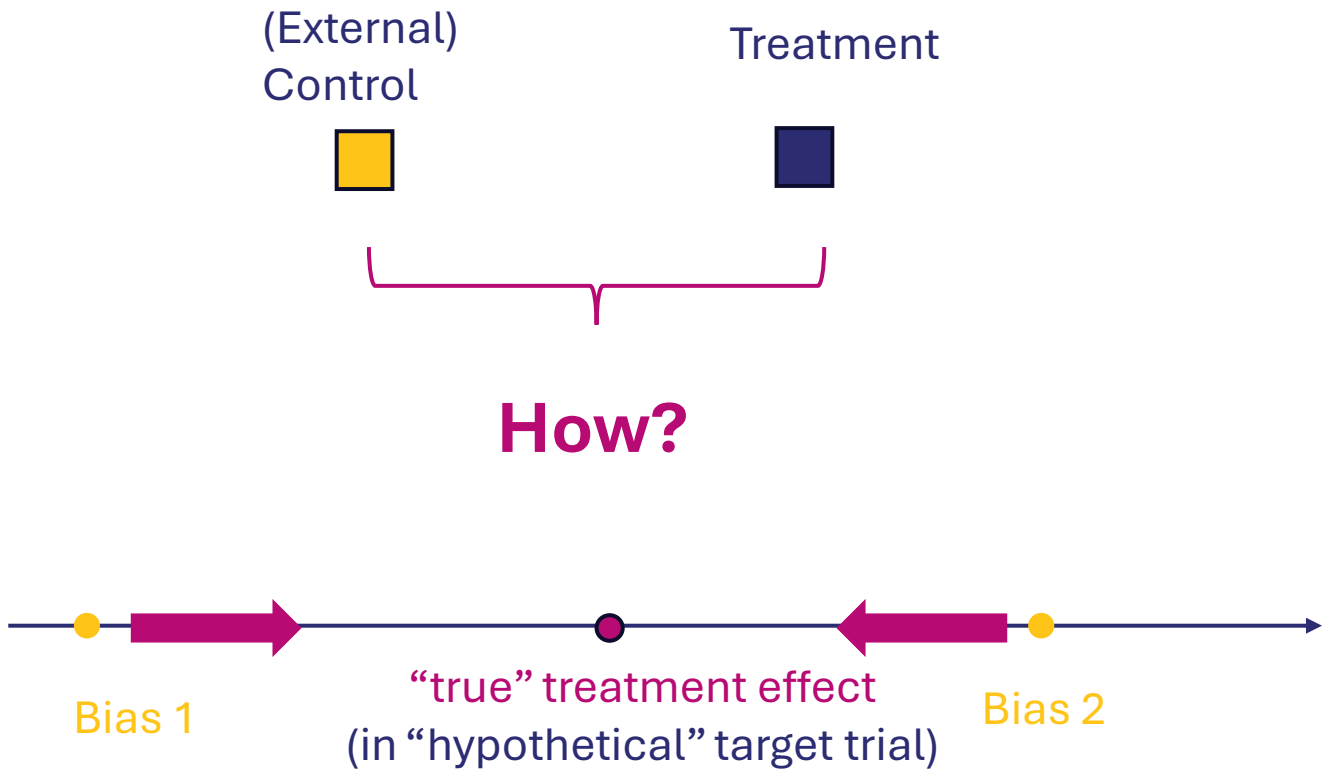
Navigating the pitfalls: reducing or mitigating biases

- **Added value:** Fair comparison of a treatment investigated in one arm in a trial to a control treatment investigated in another (external) source.
- **Pitfalls:** systematic biases* (e.g., confounding, selection, outcome assessment)
- **Methods** (design/analyses) in observational research or integrated evidence **can reduce bias.** Feasibility of these methods and trust in their results require,
  - Sufficient information on subjects and sources
  - Explicit assumptions
  - Several diagnostic checks and sensitivity analyses



*Potential sources of bias (Sterne et al 2019)

The journey of leveraging external data

Clarify purpose of using external data to the clinical trial

- What is the evidence gap?
- What is the target trial/ causal estimand?

Identify fit-for-use (external) data

- What (external) data are relevant for the comparison?
- What is the reliability of the (external) data?

Plan and implement fit-for-purpose methods

- What is the (non-randomized study) design integrating evidence?
- What analyses integrate the evidence?

Reassess and re-iterate as necessary at each step

Other similar workflows in observational research (e.g., (Desai et al, 2024), Polito et al (2024), Dahabreh et al (2024)

Case study in a rare blood disorder

Pivotal

- What is the effect of switching to iptacopan versus remaining on anti-C5 on hematological response in adult PNH patients **already on anti-C5**
- **APPLY-PNH (pivotal Ph3)** Double-blinded randomized, active control trial (iptacopan vs. anti-C5)

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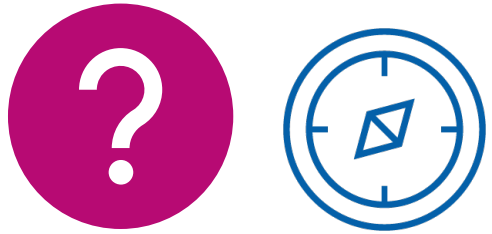
- What is the effect of iptacopan on hematological response in adult PNH patients **naive to anti-C5 treatment**?
- **APPOINT-PNH (pivotal Ph3)** single arm trial

Supportive



What is the effect of iptacopan versus anti-C5 on hematological response in adult PNH patients **naive to anti-C5 treatment**?

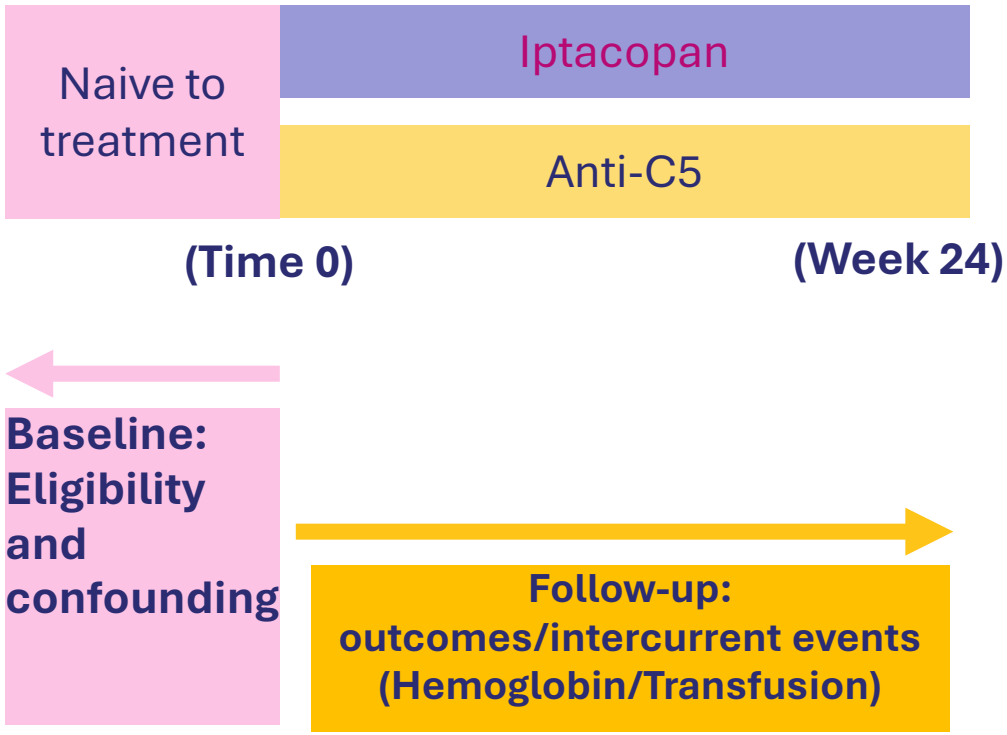
PNH: Paroxysmal Nocturnal Hemoglobinuria
Source: APPLY-PNH & APPOINT-PNH, Peffault de Latour R. et al (2024)

Case study, data and design

What is the effect of iptacopan versus anti-C5 on hematological response in adult PNH patients **naive to anti-C5 treatment**?

- **Single arm -** APPOINT-PNH (iptacopan)
- **External control –** APPEX, a PNH longitudinal “registry” from extracted medical chart review (anti-C5)

Target trial emulation



PNH: Paroxysmal Nocturnal Hemoglobunuria
Source: APPOINT-PNH, Peffault de Latour R. et al (2024); APPEX, Holt et al (2025)

Case study, summary of methods

Sources of bias	Mitigation
Selection of patients	- Emulate the target trial to align populations at time-0 prioritizing **essential** eligibility criteria
Confounding	- Identify prognostic variables by expert opinion, collect them in data sources[1] - Fit propensity score model(s) using prognostic variables,[2] balance variables using weighting[3] - Estimate the treatment effect (ATT) using a doubly robust estimator[4]
Misaligned outcome assessment schedule	Sensitivity analyses to different definitions of visit-windows

Source: APPEX, Holt et al (2025)

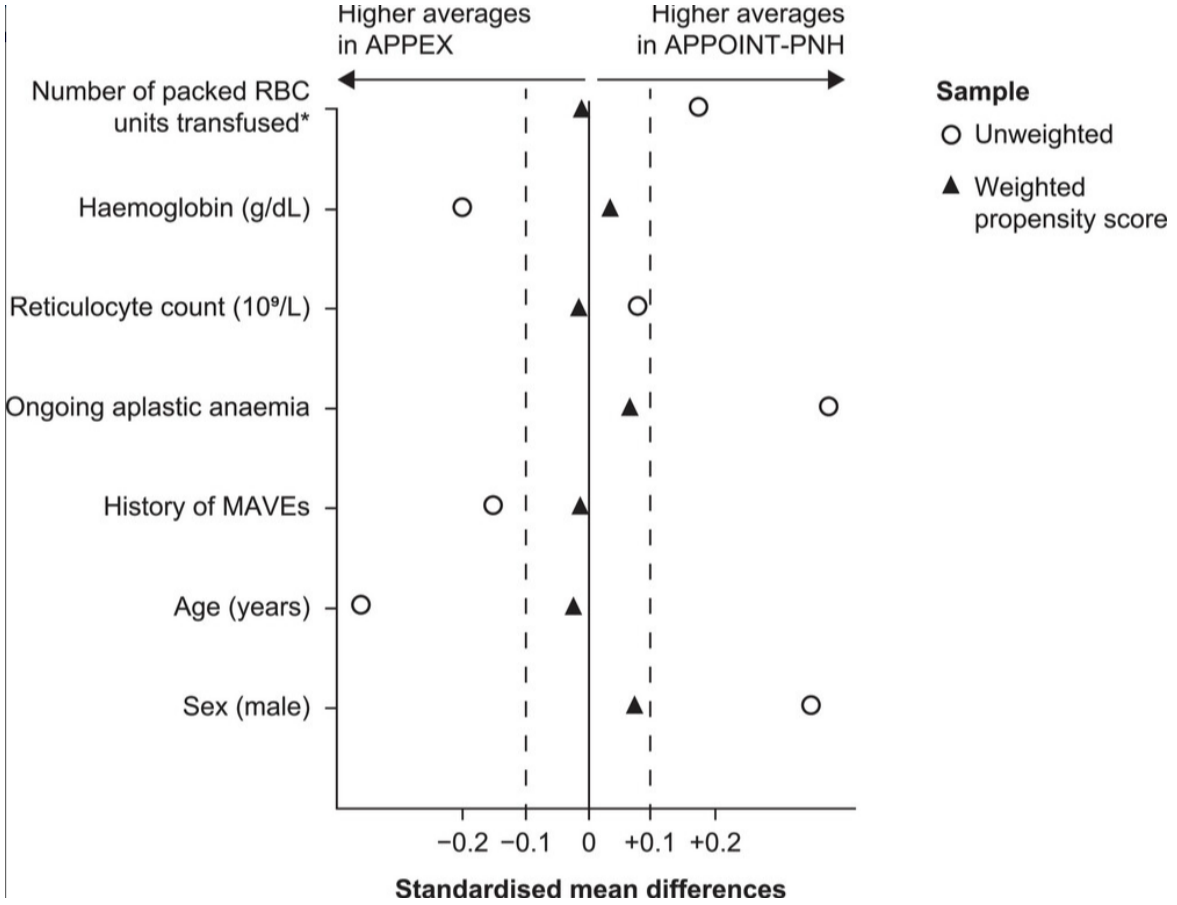
1 - evaluate the plausibility of exchangeability assumption of no unmeasured (residual) confounding

2 - evaluate the plausibility of the positivity assumption (e.g., distribution overlap of propensity scores)

3- evaluate the impact of different models on balance before/after weighting using standardized mean differences and statistical tests (Austin and Stuart 2015)

4 - ATT: average treatment on the treated weight by odds, AIPW: augmented inverse probability treatment weights (Mercatanti 2014, Chernozhukov et al 2018)

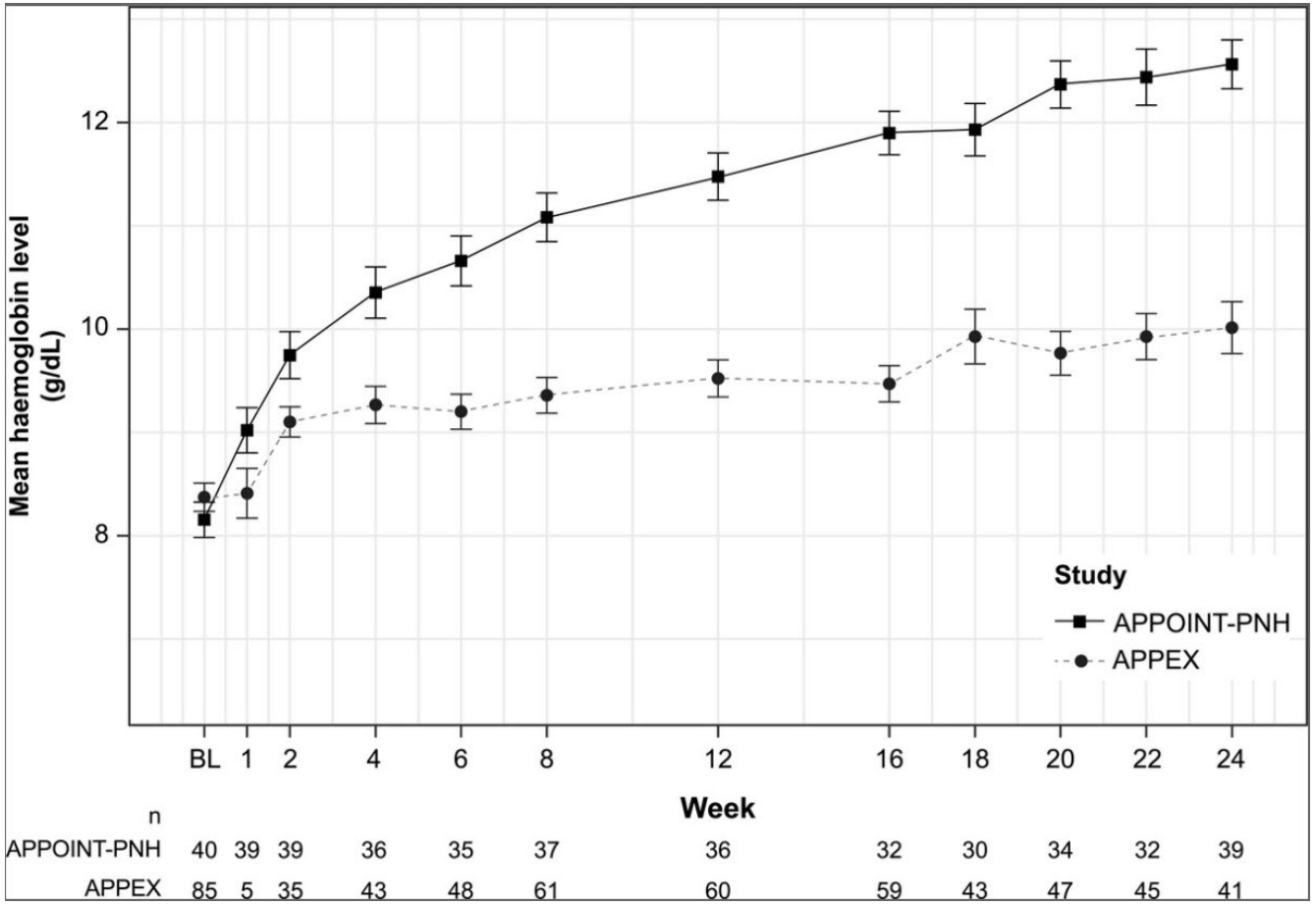
Diagnostics – potential confounding bias



Source: Holt et al (2025)

- **Potential confounding bias**: imbalance between APPEX and APPOINT-PNH on all but one prognostic factor (Reticulocyte count). The imbalance did not systematically favor one group
- **Mitigation**: methods reduced potential confounding. After adjustment, all prognostic factors are balanced

Select results (exploratory)



Source: Holt et al (2025)

- **Added value:** fair comparison of treatments and granularity of the treatment effect over time
- APPOINT-PNH (single arm) shows immediate improvement in mean hemoglobin after treatment with iptacopan, sustained until week 24
- Adjusted APPEX (external control) show small improvement after anti-C5 treatment

In summary, when making a comparison not protected by randomization

- Design and analytical strategies can **reduce bias** using eligibility and prognostic covariates with **explicit assumptions** on (dis)similarity of data sources

- **Quantitative bias/sensitivity analyses** can assess the impact of assumption violation or residual source of bias on the treatment effect estimate AND **diagnostics** can check plausibility of some assumptions

- **Challenge:** when and what to pre-specify in methods? What have we learned from similar considerations in guidance for meta-analyses (EMA 2001) and model informed drug development (ICH M15))?

Select references

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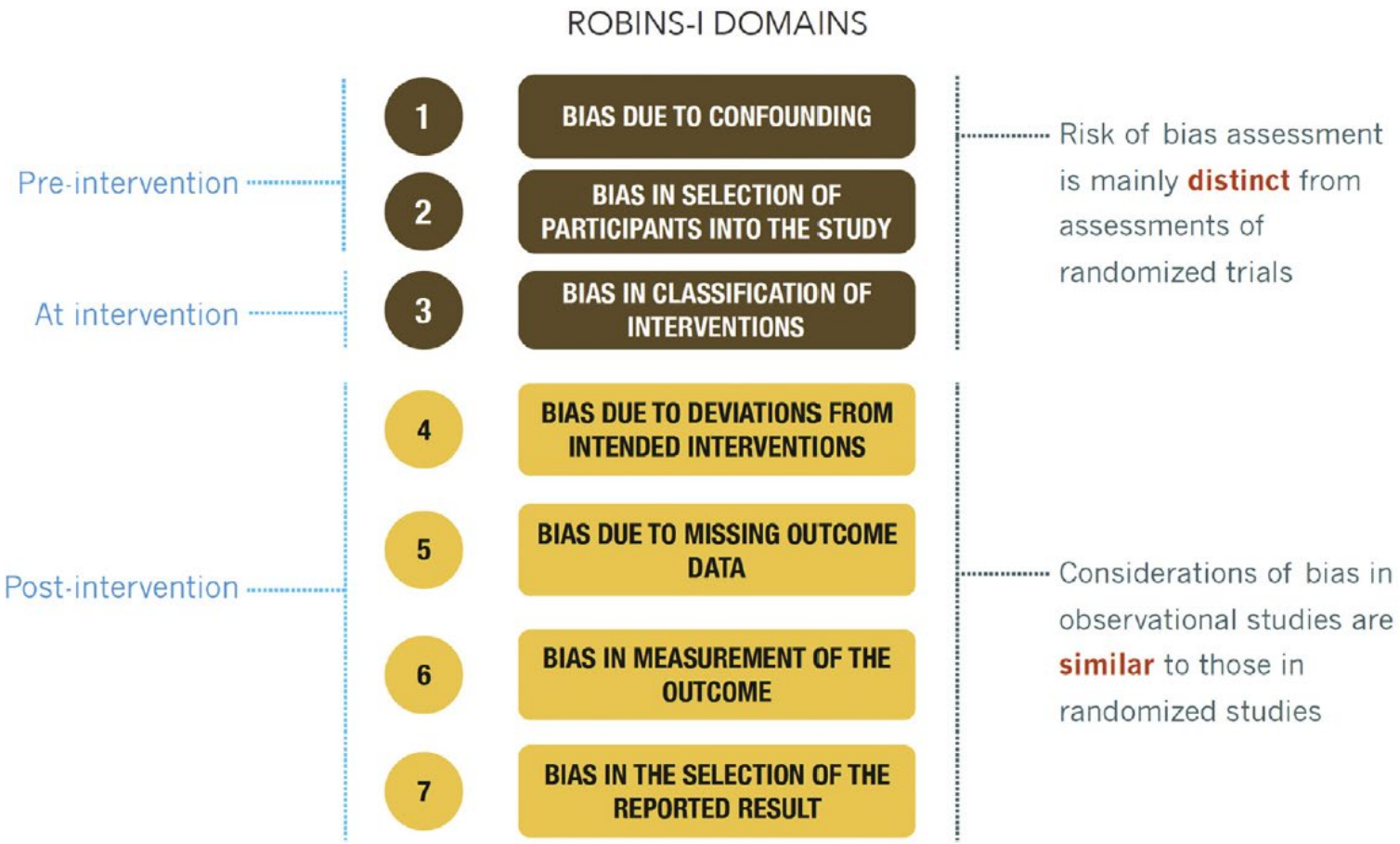
- European Medicine Agency (2001) “Points to Consider on Application with 1.Meta-analyses, 2.One-pivotal Study”
- ICH M15 (2024) Guideline on general principles for model-informed drug development (draft)

Back-up

Navigating non-randomized comparisons, naming the pitfalls or sources of bias



- confounding, or failure to account for a common cause of treatment and outcome

(e.g., frailty (external control) at baseline> single arm)

- selection, erroneously conditioning on a common effect of treatment and outcome (e.g., immortal time in single arm)

Source: Robins's I domains (Sterne J A, Hernan M A, Reeves B C et al. (2016) & Schünemann HJ et al. (2019)

Case study, minding the bias with TTE

Attributes	Target trial	Emulation in APPOINT (N=40)	Emulation in APPEX (N=85)
Population	Patients with PNH, naive to anti-C5, and with hemoglobin level < 10g/dL	More selection criteria than target trial **[Sites primarily in Asia 2021-2022]**	Same selection criteria as target trial & Age > 18 yrs **[France, UK, 2007-2022]**
Treatment	Iptacopan versus Anti-C5 therapy	Iptacopan	Anti-C5 therapy (eculizumab or ravulizumab)
Outcome(s) Intercurrent event	Hemoglobin Transfusion	Hemoglobin Transfusion	Hemoglobin Transfusion
Follow-up for outcomes (start/end)	Start of treatment until the end of study (24 weeks)	**Time-0: initiate iptacopan** **Visit schedule: weeks (1,2, 4, 6, 8, 12, 16, 18, 20, 22, 24)**	**Time-0: initiate anti-C5 therapy** **Visit schedule: as-needed, expected every few weeks at anti-C5 injection**

Modified from Supplementary Table S1 in Holt M et al 2025

Pitfalls: systematic bias, hypothetical examples